

### **REMARKS**

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

#### **I. Status of the Claims**

Claims 14-76 and 93-110 are currently pending.

#### **II. Response to Issues Raised by Examiner in the Office Action**

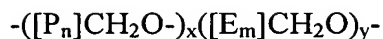
##### **A. Claim Rejections – 35 U.S.C. § 102(b)**

Claims 14, 16-38, 51-76, 93-104, and 107-110 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Wong et al., U.S. Patent No. 5,565,188 (hereinafter “Wong”). Applicants respectfully traverse this ground for rejection.

The claimed invention is directed to bioadhesive compositions of nanoparticulate active agents and methods of using the same. The bioadhesive compositions comprise active agent particles having an effective average particle size of less than about 4 microns and at least one cationic surface stabilizer. The claimed bioadhesive compositions derive their bioadhesive property, in part, from the cationic surface stabilizers. Indeed, the specification discloses “[b]ecause of the character of biological surfaces, the cationic surface stabilizers of the invention result in bioadhesive formulations.” (*See* specification at page 14, lines 11-12).

##### **1. Wong does not anticipate the claimed invention because Wong does not teach *cationic* surface stabilizers.**

Wong teaches polyalkylene block copolymers for use as surface modifiers. Such copolymers are described as “containing one or more polyoxyethylene blocks and one or more polyoxy(higher alkylene) blocks wherein at least some of the blocks are linked together by a linking group characterized in that the linking group is an oxymethylene group.” (Wong at col. 1, line 67 to col. 2, line 4). Exemplary block copolymers are provided that have the following repeating units:



wherein

P is oxypropylene;

E is oxyethylene;

n is an integer from 2 to 70, preferably from 4 to 20;

m is an integer from 2 to 250, preferably from 9 to 20;

x is an integer from 1 to 100, preferably from 1 to 10; and,

y is an integer from 1 to 100, preferably from 1 to 50.

(Wong at col. 2, lines 8-19). Upon inspection of this formula, one of skill in the art would readily see that this formula cannot carry a positive charge and thus, is not a cationic surface stabilizer.

The Examiner asserts that Wong teaches “[s]urface modifier includes cationic surface modifier such as sodium dodecyl sulfate, dioctylsulfosuccinate, or dodecyltrimethylammonium bromide (column 11, lines 10-16). Applicants respectfully disagree with the Examiner’s assertion for at least two reasons. First, as disclosed by Wong, and as is well-known to the skilled artisan, sodium dodecyl sulfate and dioctylsulfosuccinate are *anionic* surfactants. Second, in contrast to the Examiner’s assertion, Wong teaches that these ionic surfactants may be used as *cloud point modifiers* not surface modifiers. Such cloud point modifiers are used in conjunction with the polyalkylene block copolymer surface modifiers to prevent the surface modifier from dissociating from the surface of the particle. See Wong at col. 10, lines 30-38,

The cloud point is the temperature at which the surface modifier (surfactant) precipitates out of solution. By the phrase “cloud point modifier” is meant a compound which influences the cloud point of surface modifiers. In particular, the cloud point modifiers raise the cloud point of the surface modifiers in the compositions. In this way, the surface modifiers do not dissociate from the surface of the nanoparticles at temperatures used in autoclaving.

Thus, Wong does not teach the use of a cationic surface stabilizer, which is a requirement of the claimed bioadhesive compositions. Without which, as pointed out above, the compositions would lack the bioadhesive property.

Furthermore, the Examiner's assertion that "Wong teaches the use of surface modifiers having rheological properties that produced a nanoparticulate composition useful as a bioadhesive" (Office Action at page 4) supports Applicants' position that Wong does not anticipate the claimed bioadhesive composition. As taught by Wong at column 3, lines 41-44 "compositions containing these block polymers can be administered (e.g., subcutaneously or orally) as low viscosity compositions at room temperature and, when the reach physiological temperature, will tend to gel." Thus it is the properties of the block copolymers that cause them to gel at physiological temperature that give them bioadhesive properties. In contrast, the claimed bioadhesive compositions rely on the cationic surface stabilizers and their interaction with biological surfaces for the bioadhesive properties. Thus, the compositions of Wong are significantly different from the claimed bioadhesive compositions.

For at least the reasons above, Wong does not anticipate the presently claimed compositions. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

**B. Claim Rejections – 35 U.S.C. § 103(a)**

Claims 14-38, 51-76, 93-104, and 107-110 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wong in view of Pace et al., U.S. Patent No. 6,177,103 (hereinafter "Pace"). Applicants respectfully traverse this ground for rejection.

**1. Pace does not cure the deficiencies of Wong because there is no motivation to combine Wong and Pace.**

Pace teaches submicron particles of a water-insoluble or water poorly soluble compound, particularly a drug, prepared by simultaneously stabilizing a microparticulate suspension of the compounds with surface modifier molecules and rapidly expanding the suspensions into an aqueous medium from a compressed solution of the compound and surface modifiers in a liquefied gas. See Abstract and col. 5, lines 14-21, of Pace. Examples of suitable surface modifiers include natural surfactants, nonionic surfactants, anionic surfactants, cationic surfactants, colloidal clays, and natural or synthetic phospholipids. There is no mention of the use of cationic surfactants in the making of a bioadhesive nanoparticulate composition.

Pace does not remedy the deficiencies of Wong because there is no motivation to combine the two references. Specifically, there is no motivation for a skilled artisan to select the cationic surfactants from the numerous categories of acceptable surface modifiers disclosed in Pace. Moreover, given the two dramatically different processes described by Wong and Pace to make small particle compositions, one of skill in the art would not have been motivated to take aspects of the Pace process to modify the Wong process.

**2. There is no expectation of success in selecting cationic surface modifiers for use with nanoparticulate active agents to make a composition having bioadhesive properties**

There is no teaching in either Wong or Pace that a cationic surfactant when used as a surface modifier in conjunction with a nanoparticle of less than about 4 microns would result in a composition having bioadhesive properties. Indeed, the bioadhesive properties are surprising and therefore, one skilled in the art would have had no expectation of success in the making of a bioadhesive composition from the teachings of Wong and Pace.

Thus, one of skill in the art would have had no expectation of success in selecting cationic surfactants and employing the teachings of Wong. *See* MPEP § 2143.02. Accordingly, Wong and Pace fail to render the claimed invention obvious. For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**C. Claim Rejections – 35 U.S.C. § 103(a)**

Claims 39-50, 105, and 106 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wong in view of Mantelle et al., U.S. Patent No. 6,316,022 (hereinafter “Mantelle”). Applicants respectfully traverse this ground for rejection.

**1. Mantelle does not cure the deficiencies of Wong because it does not teach cationic surface stabilizers.**

The Examiner relies on Mantelle for the teaching of a water-soluble therapeutic active agent (Office Action at page 5). This, however is irrelevant to the deficiencies of Wong as described above. Therefore, Mantelle does not cure the deficiencies of Wong.

Accordingly, Wong and Mantelle fail to render the claimed invention obvious. For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

**IV. Conclusion**

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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Date

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